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<p>(21) International Application Number: PCT/EP98/03180</p> <p>(22) International Filing Date: 22 May 1998 (22.05.98)</p> <p>(30) Priority Data: 9710632.2 22 May 1997 (22.05.97) GB 9710525.8 22 May 1997 (22.05.97) GB </p> <p>(71) Applicant (<i>for all designated States except US</i>): THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): BARRETT, David, Michael [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). JONES, Huw, Lyn [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). JONES, Idwal [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). SMITH, Carl, Simon [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB).</p> <p>(74) Agent: THACKER, Michael, Anthony; The Boots Company plc, Group Patents Dept., D31, 1 Thane Road West, Nottingham NG2 3AA (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: PHARMACEUTICAL COMPOSITIONS OF FLURBIPROFEN AND BURN-MASKING AGENT FOR TREATING SORE THROAT</p> <p>(57) Abstract</p> <p>The present invention relates to pharmaceutical compositions comprising a combination of flurbiprofen with (a) a therapeutically effective amount of one or more active ingredients selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral compound, an antibiotic compound, an antifungal compound, minerals and vitamins and/or (b) a burn-masking amount of an agent which has a warming effect on the mucosa of the throat for use in the treatment of cold and flu symptoms including particularly sore throat. The treatment comprises the administration to a patient in need thereof of a pharmaceutical composition in the form of a masticable or suckable solid dosage form or a liquid or spray which releases the flurbiprofen and active ingredient(s) and/or burn-masking agent in the oral cavity so as to deliver the active components to the surface of the sore throat.</p>			

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PHARMACEUTICAL COMPOSITIONS OF FLURBIPROFEN AND BURN-MASKING AGENT FOR TREATING SORE THROAT

The present invention relates to new pharmaceutical compositions containing the non-steroidal anti-inflammatory drug flurbiprofen which also has analgesic and antipyretic activity. The invention also relates to the use of 5 these new pharmaceutical compositions in the treatment of the symptoms of colds and flu, particularly sore throat. The flurbiprofen molecule exists in two enantiomeric forms and the term flurbiprofen as used herein is intended to embrace the individual enantiomers and mixtures thereof in any proportion including a 1:1 mixture which is herein referred to as the racemic form. 10 Flurbiprofen can exist in the form of pharmaceutically acceptable salts or in the form of derivatives such as esters and such salts or esters are embraced by the term flurbiprofen as used herein.

Flurbiprofen would be expected to cause an unpleasant burning sensation at the back of the mouth when retained in the mouth. This would 15 clearly be unacceptable to the patient being treated. The present applicants have surprisingly found that an unacceptable burning sensation is not experienced when the pharmaceutical compositions of the present invention are used to treat the symptoms of colds and flu, particularly sore throat, but that the patient does receive relief of the symptoms of the cold or flu eg sore 20 throat.

A first aspect of the present invention provides pharmaceutical compositions comprising a combination of a therapeutically effective amount of flurbiprofen with a therapeutically effective amount of one or more active ingredients selected from an antihistamine, a cough suppressant, a 25 decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral compound, an

antibiotic compound, an antifungal compound, minerals and vitamins in the form of a masticable or suckable solid dosage form or a liquid or a spray.

Suitable antihistamines include acrivastine, azatadine, buclizine, cetirizine, cinnarizine, clemastine, loratadine and pharmaceutically acceptable salts thereof.

Suitable cough suppressants include codeine, dextromethorphan or pholcodine and pharmaceutically acceptable salts thereof.

Suitable decongestants include pseudoephedrine, phenylpropanolamine and phenylephrine and pharmaceutically acceptable salts thereof.

Suitable expectorant include acetylcysteine, ammonium chloride, carbocysteine, guaifensin and potassium citrate.

A suitable muscle relaxant is methocarbamol.

Suitable centrally acting analgesics include codeine and its salts and hydrocodone.

Suitable local anaesthetics include benzocaine, lignocaine, mepivacaine, prilocaine, and pharmaceutically acceptable salts thereof.

Suitable antibacterial compounds include amylmetacresol, dichlorobenzyl alcohol, quaternary ammonium compounds such as cetrimide, 20 or benzalkonium chloride.

Suitable antiviral compounds include zinc salts (for example, the acetate, gluconate and ascorbate salts), acyclovir and its sodium salt.

A suitable antibiotic is metronidazole.

Suitable antifungal compounds include nystatin, amphotericin, imidazoles such as miconazole and triazoles such as fluconazole.

Suitable minerals include zinc and selenium salts.

5 Suitable vitamins include vitamins A, C, D, E and K, sodium ascorbate, riboflavin and thiamine hydrochloride.

The above mentioned active ingredients are well known in the field of pharmacy and the dose of each to be given can be found from standard reference books. See for example Martindale The Extra Pharmacopoeia 29th
10 Edition published by The Pharmaceutical Press the disclosure of which is herein incorporated by reference.

A further aspect of the present invention provides pharmaceutical compositions comprising a combination of a therapeutically effective amount of flurbiprofen with a burn-masking amount of an agent which has a warming
15 effect on the mucosa of the throat in the form of a masticable or suckable solid dosage form or a liquid or a spray. Suitable warming agents include ginger, chilli and agents containing or consisting of anethole.

Anethole (1-methoxy-4-(1-propenyl)benzene or p-propenylanisole) is found naturally as the chief constituent of anise oil, star anise oil and fennel
20 oil. It can be incorporated into the compositions in the present invention in substantially pure form, produced either by extraction from the above oils or synthetically, or it may be incorporated as one of the above oils. The amount of anethole should be such that the required amount of taste masking is obtained.

The compositions of the present invention are intended for use in the treatment of the symptoms of colds and flu including particularly sore throat by the administration to a patient in need thereof of a pharmaceutical composition according to the present invention in the form of a masticable or suckable solid dosage form or a liquid or a spray containing a therapeutically effective amount of flurbiprofen which releases the flurbiprofen in the oral cavity so as to deliver the flurbiprofen to the surface of the sore throat.

The solid dosage form may be a lozenge which is intended to be sucked by the patient or a masticable or suckable tablet, capsule, pastille or gum, for example chewing gum. The term "lozenge" as used herein is intended to embrace all dosage forms where the product is formed by cooling a sugar-based or sugar alcohol based (eg isomalt) molten mass containing the active material. The term "tablet" as used herein is intended to embrace unit dosage forms made from compressed powders or granules or compressed pastes. A preferred pharmaceutical composition is a lozenge prepared by cooling a heated lozenge base containing the flurbiprofen and active ingredient(s) and/or burn-masking agent and other excipients to form solid lozenges.

The therapeutically effective amount of the flurbiprofen has been found to be from 5% to 40% of the normal adult dose of the flurbiprofen when given by ingestion to achieve a systemic antiinflammatory and/or analgesic effect. The flurbiprofen may therefore be present in the pharmaceutical composition in an amount from 2.5 to 20mg preferably 5 to 12.5mg, more preferably about 8.75mg. Where a pharmaceutically acceptable salt of the flurbiprofen is used; the amount of the salt used should be such as to provide the desired amount of flurbiprofen. Suitable salts include the alkali metal salts eg the sodium salt or amino acid salts eg the lysine, arginine or meglumine salts.

Solid dosage forms may be prepared by methods which are well known in the art for the production of lozenges, tablets, capsules or chewing gums and may contain other ingredients known in such dosage forms such as acidity regulators, opacifiers, stabilising agents, buffering agents, flavourings, sweeteners, colouring agents, buffering agents, flavourings, sweeteners, colouring agents and preservatives. Any additional ingredient which is added should not react with any other component of the pharmaceutical compositions of the present invention. If such interactions are possible the components concerned should be kept separate for example by encapsulating one or both of the possibly reacting components, by including one of the components in a coating applied to the lozenge after manufacture or by having the components in different layers of a multilayer product. For example, if the flavour or component of the flavour or an excipient or carrier for the flavour contains an alcohol moiety, there is the possibility of esterification of the carboxylic acid moiety in the flurbiprofen. Such esterification can be prevented or minimised by the methods outline above.

The preferred solid formulations of the present invention may be prepared as lozenges by heating the lozenge base under vacuum to remove excess water. The lozenge base may be a sugar-based or sugar alcohol-based composition. If the lozenge base is sugar-based, it may comprise a single sugar (eg sucrose) or a mixture of sugars (eg a mixture of sucrose and glucose). If the lozenge base is sugar-alcohol based it may comprise sorbitol, xylitol, maltitol, maltitol syrup, lactitol, mannitol or mixtures thereof which may be in the form of the free sugar alcohols, derivatives thereof or mixtures thereof. One preferred lozenge base comprises an approximately equimolar mixture of alpha-D-glucopyranosyl-1,6-D-sorbitol and alpha-D-glucosopyranosyl-1,1-D-mannitol (isomalt) optionally in conjunction with a hydrogenated glucose syrup such as lycasin. The lozenge base is preferably heated to a temperature in the range 110 to 170°C under vacuum.

- to remove water to give a moisture content which is preferably less than 2%, more preferably less than 1% before the remaining components of the pharmaceutical lozenge formulation are added. The remaining ingredients may be blended into the lozenge base mixture as powders or liquids.
- 5 Powders may be granulated prior to the mixing step. The molten mixture may then be passed to individual moulds in which each lozenge is formed or may be drawn into a continuous cylindrical mass from which the individual lozenges are formed. The lozenges are then cooled, subjected to a visual check and packed into suitable packaging. One form of suitable packaging is a blister pack of a water-impermeable plastics material (eg polyvinylchloride) closed by a metallic eg aluminium foil. The patient removes the lozenge by applying pressure to the blister to force the lozenge to rupture and pass through the metal foil seal. Lozenges will normally be sucked by the patient to release the flurbiprofen.
- 15 Masticable solid dose formulations may be made by the methods used to prepare chewable candy products or chewing gums. For example, a chewable solid dosage form may be prepared from an extruded mixture of sugar and glucose syrup to which the flurbiprofen has been added with optional addition of whipping agents, humectants, lubricants, flavours and colourings. (See Pharmaceutical Dosage Forms: Tablets, Volume 1, Second Edition edited by H A Lieberman, L Lachman and J B Schwartz published in 1989).
- 20 Liquid and spray formulations may be prepared by dissolving or suspending the flurbiprofen in a liquid medium which may also contain other ingredients such as stabilising agents, buffering agents, flavourings, sweeteners, colouring agents, buffering agents, flavourings, sweeteners, colouring agents and preservatives. The formulation may then be packaged into an appropriate container. For example a spray may be prepared by dissolving water soluble components in water and non-water soluble

5 ingredients in a co-solvent (eg alcohol). The two phases are then mixed and the resulting mixture filtered and placed into dispensing containers. The dispensing containers may be fitted with a metered, manually-operated spray mechanism or the dispenser may contain a pressurised propellant and be fitted with a suitable dispensing valve.

One form of preferred formulations for use in the present invention are compositions which can be sucked or chewed by the patient and which slowly release the flurbiprofen and any active ingredient and/or burn-masking agent. The flurbiprofen and active ingredient then pass over the mucous membrane 10 of the throat where some is absorbed providing topical relief. The unabsorbed flurbiprofen and active ingredient is then ingested by the patient and absorbed into the blood stream. The flurbiprofen so absorbed can act systematically to provide analgesia, anti-inflammatory and anti-pyretic activity in addition to the relief that comes from the topical application of flurbiprofen to the mucous 15 membrane of the throat. Any active ingredient present may also exert its pharmacological effect systemically.

A second form of preferred formulations for use in the present invention are sprays which are administered so that the liquid composition is brought into contact with the mucous membrane of the throat so that some of 20 the active components of the composition (the flurbiprofen and other active ingredients) and/or burn-masking agent is absorbed providing topical relief. Ingestion of the liquid composition then means that the unabsorbed flurbiprofen can be absorbed in to the blood stream to provide systemic analgesic, anti-inflammatory or antipyretic activity in addition to the relief that 25 comes from the topical application of the flurbiprofen to the mucous membrane of the throat. Any active ingredient present may also exerts its pharmacological effect systemically.

The invention will be illustrated by the following Examples which are given by way of example only. The component identified in Examples 1 to 3 as "Active ingredient" can be any one or more of the active ingredients selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antibiotic compound, an antifungal compound, an antiviral compound, minerals and vitamins. Particularly preferred active ingredients are any one or more of the compounds specifically identified hereinbefore.

10

Example 1

Lozenges are prepared containing the following ingredients expressed as the weight in milligrammes per lozenge.

	Racemic flurbiprofen	8.75
15	Calcium Carbonate	7.5
	Active ingredient	q.v.
	Solids from a 1:1 mixture of sugar and liquid glucose	to 2350

20 The mixture of the sugar and liquid glucose is heated to 140° and a vacuum applied to reduce the water content of the mixture. The flavouring is added in a sealed vessel. The flurbiprofen, the active ingredient and the calcium carbonate are blended and the blend added to the remainder of the ingredients. The resulting mixture is cooled and formed into a continuous cylindrical mass from which the individual lozenges are formed. The individual solid lozenges are visually inspected and then packed.

25 The resulting lozenges provide palatable, stable, and effective treatment for the symptoms of colds and flu particularly including sore throats.

Example 2

A mixture of flurbiprofen, the active ingredient, sorbitol and glycerin is dissolved in aqueous alcohol to provide a pharmaceutical formulation which can be packed into a dispensing container fitted with a metered
5 manually-operated spray mechanism which enables the formulation to be sprayed on to the mucous membrane of the throat as a fine spray.

Example 3

A pharmaceutical lozenge formulation is prepared containing the following
10 components expressed in milligrams per lozenge.

	Racemic Flurbiprofen	8.75
	Calcium Carbonate	7.5
	Active ingredient	q.v.
	Polyvinylpyrrolidone	1.43
15	Colloidal Silicon Dioxide (Aerosil)	0.036
	Magnesium Stearate	0.18
	Isomalt	1885
	Lycasin	440
	Anethole	q.v.

20 The flurbiprofen, the active ingredient and calcium carbonate are blended for two minutes and the blend granulated with a solution of the polyvinylpyrrolidone in isopropanol. The granules are dried and the colloidal silicon dioxide and magnesium stearate are added and the resulting mixture blended for five minutes. A molten lozenge base is prepared by dissolving the
25 isomalt in the minimum amount of water. The lycasin is added and the mixture

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heated at 110-120°C. The mixture is then heated to 145°C under vacuum to remove water to give the molten lozenge base. The blended granule and the anethole are then added to the molten lozenge base. The resulting mixture is cooled and formed into a continuous cylindrical mass from which individual
5 lozenges are prepared.

Example 4

Lozenges are prepared containing the following ingredients expressed as the weight in milligrammes per lozenge.

	Racemic flurbiprofen	8.75
10	Flavouring (orange)	1.645
	Flavouring (grapefruit)	3.75
	Calcium Carbonate	7.5
	Anethole	5.184
	Solids from a 1:1 mixture of sugar	to
15	and liquid glucose	2350

The mixture of sugar and liquid glucose is heated to 140°C and a vacuum applied to reduce the water content of the mixture. The flavouring is added in a sealed vessel. The flurbiprofen and calcium carbonate are blended
20 and the blend and flavourings are added to the remainder of the ingredients. The resulting mixture is cooled and formed into a continuous cylindrical mass from which the individual lozenges are formed. The individual solid lozenges were visually inspected and then packed.

The resulting lozenges provide palatable, stable and effective
25 treatment for symptoms of colds and flu, particularly including sore throat.

Example 5

A mixture of racemic flurbiprofen, anethole, sorbitol and glycerin is dissolved in aqueous alcohol to provide a pharmaceutical formulation which can be packed into a dispensing container fitted with a metered
5 manually-operated spray mechanism which enables the formulation to be sprayed on to the mucous membrane of the throat as a fine spray.

Example 6

A pharmaceutical lozenge formulation is prepared containing the
10 following components expressed in milligrams per lozenge.

	Racemic Flurbiprofen	8.75
	Calcium Carbonate	7.5
	Polyvinylpyrrolidone	1.43
	Colloidal Silicon Dioxide (Aerosil)	0.036
15	Magnesium Stearate	0.18
	Isomalt	1885
	Lycasin	440
	Anethole	q.v.

The flurbiprofen and calcium carbonate are blended for two minutes
20 and the blend granulated with a solution of the polyvinylpyrrolidone in isopropanol. The granules are dried and the colloidal silicon dioxide and magnesium stearate are added and the resulting mixture blended for five minutes. A molten lozenge base is prepared by dissolving the isomalt in the minimum amount of water. The lycasin is added and the mixture heated at
25 110-120°C. The mixture is then heated to 145°C under vacuum to remove water to give the molten lozenge base. The blended granule and the anethole are then added to the molten lozenge base. The resulting mixture is cooled

and formed into a continuous cylindrical mass from which individual lozenges are prepared.

The effectiveness of the treatment can be demonstrated by means of clinical trials in which patients suffering from sore throats are administered the
5 formulations described in any one of the Examples or a placebo. The patient is asked to assess the effectiveness of the treatment on parameters such as the relief of the pain associated with the sore throat, the reduction in the swelling of the throat and/or the improvement in swallowing following treatment. The patients are also examined by a clinician to determine the
10 amount of tonsillopharyngitis.

Claims

1. A pharmaceutical composition comprising a combination of a therapeutically effective amount of flurbiprofen with (a) a therapeutically effective amount of one or more active ingredients selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral compound, an antibiotic compound, an antifungal compound, minerals and vitamins and/or (b) a burn-masking amount of an agent which has a warming effect on the mucosa of the throat said composition being in the form of a masticable or suckable solid dosage form or a liquid or a spray.
2. The use of a combination of a therapeutically effective amount of flurbiprofen with (a) a therapeutically effective amount of one or more active ingredients selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral compound, an antibiotic compound, an antifungal compound, minerals and vitamins and/or (b) a burn-masking amount of an agent which has a warming effect on the mucosa of the throat for the preparation of a medicament in the form of a masticable or suckable solid dosage form or a liquid or spray intended to release the flurbiprofen in the oral cavity so as to deliver the flurbiprofen to the surface of the throat for the treatment of sore throat.
3. A method of treating a sore throat comprising the administration of a pharmaceutical composition in the form of a masticable or suckable solid dosage form or a liquid or spray, said pharmaceutical composition comprising a combination of a therapeutically effective amount of flurbiprofen with (a) a therapeutically effective amount of one or more active

5 ingredients selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral compound, an antibiotic compound, an antifungal compound, minerals and vitamins and/or (b) a burn-masking amount of an agent which has a warming effect on the mucosa of the throat to the surface of the sore throat .

4. A composition, use or method as claimed in any preceding claim wherein
10 the antihistamine is selected from acrivastine, azatadine, buclizine, cetirizine,- cinnarizine, clemastine and pharmaceutically acceptable salts thereof;

the cough suppressant is selected from codeine, dextromethorphan or pholcodine and pharmaceutically acceptable salts thereof;

15 the decongestant is selected from pseudoephedrine, phenylpropanolamine and phenylephrine and pharmaceutically acceptable salts thereof.

the expectorant is selected from acetylcysteine, ammonium chloride, carbocysteine, guaifensin, potassium citrate;

the muscle relaxant is methocarbamol,

20 the centrally acting analgesic is selected from codeine and its salts and hydrocodone;

the local anaesthetics is selected from benzocaine, lignocaine, mepivacaine, prilocaine and pharmaceutically acceptable salts thereof;

25 the antibacterial compounds is selected from amylmetacresol, dichlorobenzyl alcohol, quaternary ammonium compounds such as cetrimide, or benzalkonium chloride;

the antiviral compounds is selected from zinc salts (for example the acetate, gluconate and ascorbate salts), acyclovir and its sodium salt,

the antibiotic compound is metronidazole;

30 the antifungal compound is selected from nystatin, amphotericin, miconazole and fluconazole.

the mineral is selected from zinc and selenium salts; and
the vitamin is selected from vitamins A, C, D, E and K, sodium
ascorbate, riboflavin and thiamine hydrochloride.

- 5 5. A composition, use or method as claimed in any preceding claim in
 which the warming agent contains or consists of anethole.
6. A composition, use or method as claimed in any preceding claim
 wherein the amount of flurbiprofen is from 2.5 to 20 mg per unit dose.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/03180

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 6 A61K9/20 A61K9/08 A61K31/19		
<p>According to International Patent Classification(IPC) or to both national classification and IPC</p>		
B. FIELDS SEARCHED <p>Minimum documentation searched (classification system followed by classification symbols)</p> <p>IPC 6 A61K</p>		
<p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p>		
<p>Electronic data base consulted during the international search (name of data base and, where practical, search terms used)</p>		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 94 14476 A (PROCTER & GAMBLE) 7 July 1994 see page 1, line 28 - line 33 see page 4, line 19 - line 32 ---</p>	1-4, 6
P, X	<p>WO 97 18802 A (BOOTS CO PLC ;BARRETT DAVID MICHAEL (GB); SMITH CARL SIMON (GB); T) 29 May 1997 see page 8; example 14 see page 5; examples 1-4 ---</p>	1-3, 6
Y	<p>WO 97 02273 A (PROCTER & GAMBLE) 23 January 1997 see page 7, line 19 - line 22 see page 8, line 33 - line 37 see page 9, line 24 - page 10, line 2 ---</p>	1-6 -/-
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.
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<p>Date of the actual completion of the international search</p> <p>29 September 1998</p>		<p>Date of mailing of the international search report</p> <p>30/10/1998</p>
<p>Name and mailing address of the ISA</p> <p>European Patent Office, P.B. 5018 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax. (+31-70) 340-3016</p>		<p>Authorized officer</p> <p>Boulois, D</p>

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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